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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/001,245	HOLM ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,25,26,28,35,37-39,64 and 66-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22,25,26,28,35,37-39,64 and 66-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received December 12, 2006 are acknowledged.

Claims 23, 24, 27, 29-34, 36, 40-63, and 65 have been canceled.

Claims 22 and 37 have been amended.

Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 are pending and under examination as they read on recombinant mutant allergens

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-96 of copending Application No. 10/719,553. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims arrive at similar allergenic variants, and by what appears to the Examiner by the same method of selection, or if not by an obvious variant thereof. Specifically, Claims 36-96 teach a mutant Bet v 1 allergen with 1 or more substitutions, wherein said substitutions occur at many amino acid residues that are identical between

the '719 application and the instant application, such as those recited in copending claim 37 and instant claim 22.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant has acknowledged this provisional rejection and has asked that it be held in abeyance at this time.

The rejection is maintained.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. The rejection of claims 1-22, 25, 26, 28, 35, 64, and 66-82 under 35 U.S.C. 103(a) as being unpatentable over Ipsen et al., (US 2004/0091500 A1, of record, see entire document) has been withdrawn in view of applicant's statement. Specifically, in the reply received December 12, 2006, applicant states:

> "Applicant confirms that all inventors of the subject matter disclosed and claimed in the '553 patent and all inventors of the subject matter disclosed and presently claimed in the instant application were at all times subject to an obligation of assignment to ALK Abello A/S."

Application 10/719,553 (the '553 patent) has published as US 2004/0091500 A1. Since US 2004/0091500 A1 only qualifies as prior art under 35 USC 102(e), this rejection has been withdrawn.

6. Claims 1-22, 25, 26, 28, 35, 64, and 66-82 stand rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/47680 (Reference 1 on the IDS submitted 3-7-02, see entire document) for the reasons of record.

The office action mailed July 14, 2006 states:

> Ipsen et al. (US 2004/0091500 A1) teach recombinant mutant allergens, pharmaceutical compositions comprising said allergens and excipients, and methods of their production (see entire document, particularly the abstract and paragraph 68). These mutant allergens are derived from naturally occurring allergens and comprise substitution mutations at conserved surface-exposed positions among homologous, taxonomically related proteins with a non-conservative amino acid replacement such that the specific binding capacity of the mutant allergen is reduced in comparison to the naturally occurring allergen (see particularly paragraphs 49-55). These mutant allergens are to be made from numerous allergens, including allergens from birch pollen, *Dematophagoides* mites, and animals such as dogs, cat and horses (see particularly paragraphs 56 and 57). The recombinant allergens can comprise one or more substitution mutations (paragraphs 58, 60, 65 and 66) and a working example is provided that comprises four mutations (paragraph 159). Positions to be mutated in the birch tree pollen Bet v 1 comprise substitution at positions 10, 25, 28, 32, 45, 47, 55, 77, and 108, many of the same positions recited in instant claim 22 (see paragraph 58). The substitution mutations are taught as being located in a surface exposed patch that is about 400 angstroms, which happens to be the area covered by an antibody upon binding (see particularly paragraphs 76-81 and 94). The mutants of Ipsen et al. comprise an α-carbon backbone tertiary structure that is essentially the same as the naturally occurring allergen (paragraph 48), and compositions comprising more than one mutant allergen are disclosed (paragraphs 70-74). The data obtained from the working examples of Ipsen indicate that T cell epitopes are maintained and demonstrate a correlation between increasing numbers of mutations and reduced IgE reactivity, with the greatest reduction taking place in the mutant comprising four mutations (see particularly paragraphs 112-167, most particularly paragraph 165). Note that Ipsen et al. did not actually make mutants comprising in excess of four mutations.
>
> These teachings differ from the instant claimed invention in that Ipsen et al. do not teach the spacing of their allergen mutations and did not make a Bet v 1 mutant allergen that comprises mutations at all of the residues discussed above. However, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make a recombinant mutant Bet v 1 allergen comprising all of these mutations. Motivation to do so comes from the disclosure of Ipsen et al. that Bet v 1 mutants are to comprise multiple mutations and the data of Ipsen et al. which indicate that IgE reactivity decreases as the number of mutations are increased. A person of ordinary skill in the art would have a reasonable expectation of success in making such a mutant based on the numerous working examples of mutant Bet v 1 molecules taught by Ipsen et al.
>
> Note that Ipsen et al. do not teach the spacing of the positions to be mutated relative to each other in the three dimensional structure of Bet v 1. The instant specification teaches that primary and secondary mutations of the instant invention are to be selected from a group that comprises the positions disclosed by Ipsen et al. (see particularly lines 10-17 of the instant specification) and further teaches that primary mutations and secondary mutations can occur at the same amino acid position (see particularly lines 5-8 of page 25). As such a mutant Bet v 1 allergen comprising all mutations at all 9 of the positions taught by Ipsen et al. would minimally comprise 4 primary mutations that are at least 15 angstroms apart.
>
> The disclosure of WO 99/47680 is identical to that of US 2004/0091500 A1, differing only in pagination and publication date. As such, the indicated claims are rejected for the same reasons as discussed above in conjunction with the disclosure of US 2004/0091500 A1.

Applicant's arguments filed December 12, 2006 have been fully considered but they are not persuasive. Applicant argues that even though elements, such as specific recited mutations, are disclosed by Ipsen et al. there is no motivation to combine these mutations and that there is no disclosure that such a combination results in a circular surface region of 800 square angstroms that does not comprise a mutation.

These arguments are not persuasive. Applicant argues that there is no direct motivation to combine single point mutations disclosed by Ipsen et al. to derive a mutant allergen comprising multiple mutations. The courts have stated that "motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. *In re Dembiczak*, 175 F.3d 994, 999 [50 USPQ2d 1614] (Fed. Cir. 1999). As we explained in *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1472 [43 USPQ2d 1481] (Fed. Cir. 1997), "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Dystar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.* [80 USPQ2d 1641] (Fed. Cir. 2006).

Ipsen et al. disclose data indicating that IgE reactivity decreased as the number of mutations increased, with four mutations yielding the greatest reduction in reactivity (paragraphs 112-167, most particularly 165). Given that Ipsen et al. teach that recombinant allergens comprising reduced IgE binding are more desirable than the native allergen for immunotherapy, it is logical that a skilled artisan would make recombinant allergens comprising at least four mutations since the data of Ipsen et al. demonstrate that this number of mutations provided the largest observed decrease in IgE binding. As such a skilled artisan would be motivated to make a recombinant allergen comprising at least four mutations.

Applicant's argument that there is no disclosure of an 800 square angstrom area comprising no mutations is not persuasive because once an allergen comprising the above discussed mutations is made, it would comprise such a mutation free patch even

if this feature was not appreciated or fully disclosed since the structure of the allergen is governed by its amino acid sequence.

Note that the WO 99/47680 reference qualifies as art under 35 USC102(b), and as such applicant's statement that the art disclosed subject matter and the instant application were at all times subject to an obligation of assignment to ALK Abello A/S does not preclude a rejection under 35 USC 103.

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The office action mailed July 14, 206 states:

> Applicant has claimed a genus of mutant allergens and compositions comprising said allergens. These mutants can be derived from any allergen and must comprise at least 4 mutated surface-exposed amino acid residues wherein the mutations are spaced at least 15 angstroms apart. To support this genus, applicant has generated mutants of Bet v 1 comprising at least 4 mutations that have been tested for IgE binding activity (Examples 4, 9, and 10), and has indicated where such mutations are to be made in the allergens Der p 1 and Phl p 5 (see examples 5-8). The disclosure does not provide adequate written support of the claimed genus of allergens for the following reasons:
>
> The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri., January 5, 2001, see especially page 1106 column 3).
>
> The breadth of the independent claim reads upon mutants of any naturally occurring allergen, both those known and unknown in the art, and only in dependent claims 21 and 22 is the breadth narrowed to read on only one allergen. It is known in the art that no a priori structural basis can determine if a molecule will or will not be bound by IgE (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39) and as such there is no core structure found in all allergens that is responsible for IgE binding.

Therefore, disclosure of specific mutations in one particular allergen that give rise to reduced IgE binding is not applicable to other allergens. The specification does not disclose mutations for all allergens, an impossible task given that the claims read on allergens that naturally occur yet have not been identified by scientists, and adequate written description cannot be given for something that is unknown. As such, a skilled artisan would reasonably conclude that the disclosure fails to provide a representative number of species to describe the claimed genus of mutant allergen polypeptides. See *Eli Lilly*, 119 F. 3d 1559, 43, USPQ2d 1398.

Applicant's arguments filed December 12, 2006 have been fully considered but they are not persuasive. Applicant argues that Table 8 lists references for allergens that have been cloned or sequenced, while Table 9 list allergens for which three-dimensional structures were known, and as such "Thus, as of the filing date of the present application, on[e] of ordinary skill in the art would immediately recognize that the listing of allergens set forth in the specification referred to the amino acid sequences of allergens that were known and that such amino acid sequences were readily ascertainable."

This argument is not persuasive because the claims in question are not limited to the allergens disclosed in tables 8 or 9.

Applicant also argues that the exemplifications utilizing mutants of Bet v 1, Der p 1, and Phl p 5 are representative of the claimed genus of all allergens.

This argument is not persuasive, because as discussed in the rejection of record, there is no core structure present in an allergen that gives rise to "allergenicity" and as such specific mutations made for one specific allergen are not applicable to the genus of all allergens.

Applicant argues that the specification defines structural characteristics of the claimed genus, such as surface accessibility, homology, and reduced IgE binding.

This argument is not persuasive because as discussed above, the claimed genus is not limited to allergens for which sequence and three-dimensional structure data are known, thus surface accessibility and homology calculations are not applicable to the entirety of the claimed genus. IgE binding is a functional characteristic that cannot be determined by structure alone as taught by Blumenthal et al. (of record).

Therefore, a skilled artisan would conclude that applicant was not in possession of the claimed genus at the time the instant application was filed and the rejection is maintained.

9. Claims 1-22, 25, 26, 28, 35, 37-39, 64, and 66-85 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The office action mailed July 14, 2006 states:

> Applicant has claimed mutant allergens comprising mutations that are spaced at least 15 angstroms apart wherein said allergen also comprises reduced specific IgE binding capability. The specification provides working examples of such mutant allergens for the birch pollen allergen Bet v 1(Examples 4, 9, and 10), and provides guidance as to where mutations should be made in the allergens Der p 1 and Phl p 5 (see examples 5-8).
>
> The independent claim recites that comparison to homologous proteins are required in selecting the identity of the amino acid residue that is to be substituted at a position chosen for mutagenesis. It is noted that the specification defines substitution as comprising deletions and additions of single amino acids as well as single amino acid substitutions (lines 19-22 of page 42), but given that the independent claim recites "substitution of one surface-exposed amino acid residue with another residue" the mutant allergens do not comprise additions or deletions since an addition comprises two residues and a deletion does not comprise any residue. The specification does not define a particular algorithm to be used in determining homology, and it is known in the art that parameters such as gap length, substitution matrices, and percent cutoffs influence homology calculations (The Statistics of Sequence Similarity Scores, downloaded from ncbi.nlm.nih.gov/BLAST/tutorial/Altschul-1.html, see entire document). Calculations made with different parameters will identify different sets of homologous proteins, thus changing the possible amino acids available for substitution.
>
> The independent claim also recites that the mutations are required to be 15 angstroms or more apart. As such, the structure of the naturally occurring allergen must be known prior to generating the mutant allergens. The scope of the independent claim reads on all naturally occurring allergens, including those presently unidentified by scientists and physicians. The structures of all allergens are not known, and crystallization of proteins for structure determination is unpredictable and is based upon trial and error (Kundrot C.E., Cell Mol Life Sci 2004, 525-536, see entire document particularly the abstract). Further, the art teaches that correlations between structure and IgE binding (or the lack of IgE binding) cannot be predicted on an a priori structural basis (Blumenthal et al. in Allergens and Allergen Immunotherapy, 3rd edition, 2004, pages 37-50, see entire document, particularly the last sentence of the third complete paragraph of page 39). The claims recite that the mutant allergen comprises a reduced capability to bind IgE, but guidance as to what positions should be mutated in a native allergen commensurate in scope with the limitations of the instant claims appear to only be provided for the naturally occurring allergens Bet v 1, Der p 1, and Phl p 5.
>
> Dependent claims also recite that the claimed mutant allergen comprises secondary mutations in addition to comprising at least 4 primary mutations. However, the specification teaches that primary mutations and secondary mutations can occur at the same position in the sequence of an allergen, and provides examples of Bet v 1 positions that serve as both primary and secondary mutations (see particularly lines 5-8 of page 25 and lines 10-17 of page 29). Claim 22 recites specific positions in Bet v 1 that can be mutagenized, but it is not clear if any four recited positions can be used together in the claimed invention, or if only some specific subcombination of mutated positions satisfies the spacing limitations recited in the independent claim. As such, a skilled artisan would not be able to make mutant allergens comprising secondary mutations since he cannot distinguish between primary and secondary mutations, and even within the example of Bet v 1 it is not clear which combinations of mutated positions can be generated to yield a mutant allergen that meets the recited structural limitations.
>
> Therefore, based upon the breath of applicant's claimed invention, the unpredictability concerning the identity of all naturally occurring allergens, the generation of crystallographic data concerning said allergens, the correlation between IgE binding and allergen structure, the identification of amino acid residues suitable for substitution based upon homology, and the inability to distinguish primary from

secondary mutations, a skilled artisan would be unable to make and use the full breadth of applicant's claimed invention without conducting undue research.

Applicant's arguments filed December 12, 2006 have been fully considered but they are not persuasive. Applicant argues that the claims are enabled because the specification sets forth numerous examples of the claimed invention.

This argument is not persuasive because as discussed in the rejection of record, while the specification indicates where mutations are to be made in the allergens Bet v 1, Der p 1, and Phl p 5, the location of these mutations does not provide guidance or direction as to what positions are to be mutated in other allergens, including those unknown or for whom no three-dimensional structural data was know that the time the instant application was filed.

Applicant argues that even though the disclosure defines "substitution" as comprising deletion, substitution, and addition, the meaning of "substitution of one surface-exposed amino acid with another residue" is clear on its face.

The prior office action states "It is noted that the specification defines substitution as comprising deletions and additions of single amino acids as well as single amino acid substitutions (lines 19-22 of page 42), **but given that the independent claim recites "substitution of one surface-exposed amino acid residue with another residue" the mutant allergens do not comprise additions or deletions** since an addition comprises two residues and a deletion does not comprise any residue." (emphasis not in original). As such, the statement in the rejection was to clarify the scope of the claims as they are being examined. Based upon applicant's arguments, it appears that applicant agrees with this scope, and as such there is no argument since applicant and the examiner concur.

Applicant argues that the specification discloses that sequence alignments and homology calculation may be performed using the program CLUSTAL W.

This argument is not persuasive since while the exemplifications disclosed in the specification made use of this program, the specification does not appear to disclose the parameters used by this program in making alignments (i.e. gap length, substitution matrices, etc...) that are known to influence homology calculations as taught by the

BLAST tutorial. As such, it is not clear how a skilled artisan is to determine "homology" in accordance with the limitations of the instant claimed invention.

Applicant argues that a skilled artisan can distinguish primary from secondary mutations because primary mutations must be surface exposed residues that are spaced 15 angstroms apart, while secondary mutations can be located at any distance.

This argument is not persuasive because the claims read on allergens for which no sequence or three-dimensional structural data are known. In the absence of a solved protein crystal structure, how can a skilled artisan determine which residues are or are not 15 angstroms apart? Solving three-dimensional structures is not predictable as taught by Kundrot et al. (of record), and even when such a structure is known, the structure itself does not allow for prediction of IgE binding in the absence of additional data as taught by Blumenthal et al. (of record). Further, it appears that the definition of primary and secondary mutations rely upon the presence of other mutations, such that a mutation at a particular residue, say X, is a primary mutation when compared with the mutations of set A, but is a secondary mutation when compared with the mutations of set B. As such, the definition is circular since it depends on other mutations, these other mutations being primary or secondary mutations based upon additional mutations, ad infinitum. Unless a fixed reference point, such as an amino acid identified by position within a known three-dimensional structure (since the primary mutations must be surface exposed and 15 angstroms apart), is provided it does not appear that a skilled artisan can reasonably distinguish between primary and secondary mutations.

Applicant's last argument appears to be that the theory behind applicant's selection of mutagenesis positions differs from the prior art in that it allows mutation of all surface exposed epitopes not just those identified in dominant IgE binding epitopes without significantly altering the three-dimensional structure of the mutant as compared to the native allergen.

This argument is not persuasive because it does not indicate that a skilled artisan would be able to use such theory and methods disclosed in the specification to make mutants of any allergen, and the above discussion sets forth why the breadth of the

instant claimed invention cannot be made by skilled artisans without first conducting additional, unpredictable research.

The rejection is maintained.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 3, 15, 22, 37-39 and 83-85 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The office action mailed July 14, 2006 states:

> Claims 3, 15, 37-39 and 83-85 recite mutant allergens comprising secondary mutations, and compositions comprising said allergens. The criteria for the placement of the secondary mutations are the same criteria recited for the placement of the 4 primary mutations that the mutated allergen must comprise since the specification teaches that the same amino acid position can serve as a primary or secondary mutation (see particularly lines 5-8 of page 25). As such, primary and secondary mutations appear to be indistinguishable. How can a skilled artisan know if a mutant allergen comprises 4 primary mutations and some secondary mutations or if said allergen comprises more than 4 primary mutations? Further, what is the minimum number of mutations present in a recited allergen that comprises secondary mutations? Only 4 (since the primary mutations can serve as secondary mutations) or greater than 4?
>
> Claim 37 and its dependent claims also recite "recombinant mutant allergen variants according to claim 1". Claim 1 recites "recombinant mutant allergens", but does not identify said allergens as variants. As such the term variant lacks antecedent basis in the claims as currently written.
>
> Claim 22 recites N--7 as a position amenable to substitution, but what does the second hyphen mean? Is the mutation at position 7 of Bet v 1 or is it at –7, whatever that may mean? Further, the claim mixes position nomenclature in that some positions, such as V2, are not hyphenated while other including K-129 are hyphenated. Is there significance to the different nomenclatures?

Applicant's arguments filed December 12, 2006 have been fully considered but they are not persuasive. Applicant argues that the minimum number of primary and secondary mutations is 5. Applicant appears to base this on the recitation that the claimed mutant allergen comprises at least 4 mutations spaced at least 15 angstroms apart and the disclosure that secondary mutations may be close to a primary mutation (lines 5-8 of page 25).

This argument is not persuasive since as disclosed in lines 10-17 of page 29, mutations at a given position of Bet v 1 are disclosed as being primary and secondary mutations. As such, a mutant allergen comprising 5 mutations may comprise 5 primary mutations and no secondary mutations or could be interpreted as comprising 4 primary

and 1 secondary mutations since while the specification discloses that secondary mutations may be close to a primary mutation, there does not appear to be any explicit definition that a secondary mutation must be less than 15 angstroms in distance from another mutation, especially given the disclosure that primary and secondary substitution mutations are to be selected from the same group (lines 10-17 of page 29). Since there is no definition that secondary mutations must be less than 15 angstroms in distance apart and the disclosure that primary and secondary mutations can be selected from the same list, it appears reasonable that a mutant allergen comprising 4 mutations can comprise 4 primary mutations as well as secondary mutations since the primary and secondary mutations can be one in the same.

Applicant also argues that the term "variant" has been replaced in claim 37.

This argument is persuasive for claims 37 and 39, but claims 38 and 83-86 still recite "variant".

Applicant argues that claim 22 has been amended to recite a unified nomenclature.

In view of the amendments to claim 22, that part of the rejection of record has been obviated.

12. No claims are allowable.

13. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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February 27, 2007

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PRIMARY EXAMINER